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The Ophthalmic In Situ Gelling System: A Comprehensive Review

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Abstract: The eye is a delicate organ with low permeability, short precorneal residence time, and small area for absorption, which poses significant barriers to drug delivery. Traditional ocular delivery systems are constrained by tear and blinking, leading to blurred vision and untimed release events. In situ ophthalmic gels have been developed to overcome these challenges, allowing sustained drug release at the target site. These gels are in solution form before administration and convert to a gel under physiological conditions. This review discusses the anatomy and physiology of the eye, challenges of ocular drug delivery, types of in situ gelling systems, mechanisms of gel formation, types of smart polymers, and methods for evaluating polymeric in situ gels. The study aims to optimize self-assembled nanomicelles incorporating latanoprost (LAT), an anti- glaucoma drug, using a two-level, two-factor full factorial design. The nanomicelles have a spherical morphology and a 77.5% encapsulation efficiency, demonstrating sustained LAT release over 12 hours. In normotensive rabbits, the nanomicelles reduced IOP by up to 40% for three days, significantly longer than the IOP-lowering efficacy of XALATAN eye drops. These findings suggest that self-assembled nanomicelles can enhance ocular bioavailability and extend the therapeutic duration of LAT while providing physical stability.

Keywords:-Intraocular pressure, Occular drug delivery, BCS class II drug, Nanomicelles, Soluplus, Particle size distribution, in situ gel, sol-gel transition, smart polymers, sustained release

I. INTRODUCTION

Introduction

Ocular medication delivery is a complex and challenging field for pharmaceutical scientists. Ophthalmic in situ gels, often containing hydrogels, have improved over the past decade to 20 years. However, the delicate nature of the application site and numerous restrictions make it challenging to formulate medications that can pass through the eye's protective layers and reach the site of action with high concentration. Innovative drug delivery techniques aim to overcome these barriers without causing harm to permanent tissue. Common conditions treated with topical medication delivery include glaucoma, trachoma, keratitis, conjunctivitis, and blepharitis. Conventional formulations like solutions, suspensions, emulsions, and ointments have drawbacks such as poor bioavailability, increased precorneal elimination, and variability in efficacy. Optical application is the most popular formulation for ophthalmic chemotherapy due to its ease and safety.[1-3]

Anatomy of Eye

The human eye is divided into two segments: the anterior segment, which includes the cornea, conjunctiva, iris, pupil, ciliary body, anterior chamber, aqueous humor, lens, and trabecular meshwork, and the posterior segment, which includes the vitreous humor, sclera, retina, choroid, macula, and optic nerve. The cornea is the outermost membrane, composed of five layers: epithelium, Bowman's layer, stroma, Decemet's membrane, and endothelium. Aqueous humor, a clear liquid, fills the eye's anterior and posterior chambers, providing nourishment. The iris, a contractile curtain, controls the pupil's size and light intake. The central layer of the eye contains the ciliary muscle, which regulates viewing distances. The lens is a transparent biconvex structure, surrounded by tissue layers in a capsule. [4-5]

The conjunctiva is a mucous membrane that protects the eyes by lubricating them and secreting mucus. The sclera, also known as the "white of the eye," is the outer covering that maintains the eye's shape and serves as the main defense organ. The choroid, a thin, highly vascularized tissue between the retina and the sclera, absorbs excess light to prevent impaired vision. The retina is a multi-layered structure made up of nerve fibers, vascular glial cells, and neural cells. It is sensitive to light due to photosensitive cells that absorb light and transform it into electrical impulses. The vitreous humor, a transparent, thin, jelly-like fluid, is distributed between the retina and lens. Blood arteries provide nutrition to the retina's outer layers. [6-9]

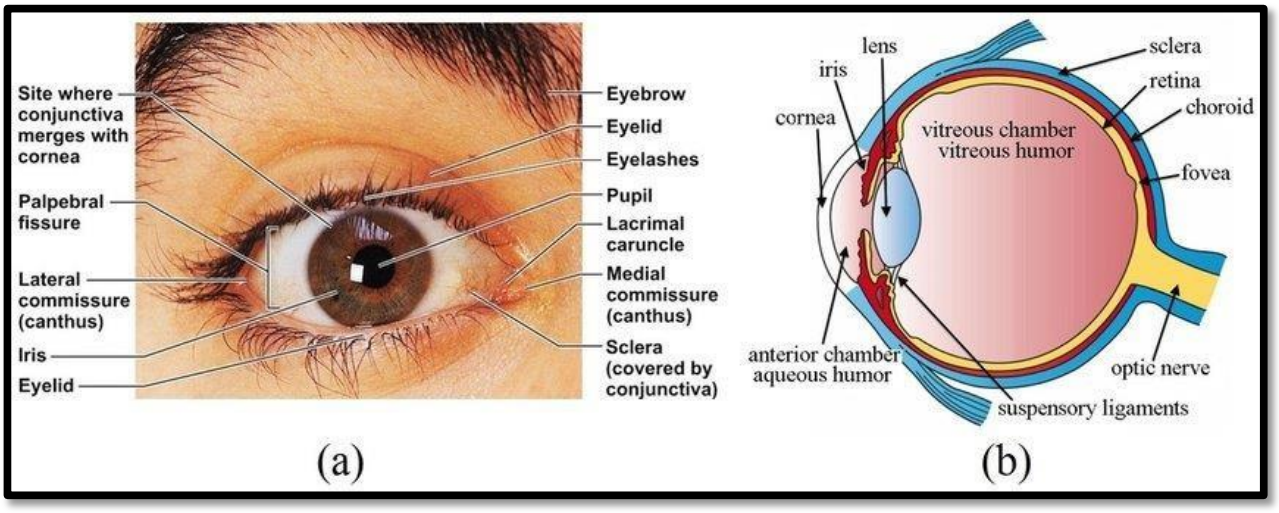

Figure: 1: Anatomy of eye

The barriers:

Drug loss from the ocular surface is a significant issue.

The drug's dosage in the ocular system causes some to be washed off by lacrimal fluid, with a washout rate of 1 µl/min. The majority is quickly removed through the nasolacrimal duct. Systemic absorption, unlike ocular absorption, is another source of drug elimination. This occurs either after fluid enters the nasal cavity or primarily through the conjunctival sac to nearby blood capillaries. [10]

Lacrimal fluid-eye barriers

The corneal epithelium in the eye restricts the amount of medication absorbed from lacrimal fluid due to tight junctions. Lipophilic medications have greater permeability in the cornea, while hydrophilic medications have a leaky epithelium. The conjunctiva, with a larger surface area and leaky epithelium, facilitates rapid systemic absorption.

Ocular-blood barriers

The bloodstream contains blood-ocular barriers, including the bloodretina barrier and blood-aqueous barrier. The anterior blood-eye barrier, made up of endothelial cells in the uvea, reduces plasma albumin entry into the aqueous humor and inhibits the entry of hydrophilic medications. The posterior barrier, made up of retinal pigment epithelium and retinal capillaries, forms a tight wall connection between the eye and plasma. The choroidal extravascular space allows easy access to medications due to the choroid vasculature's blood flow and leaky walls. [11]

The routes of ordinary drug delivery are as follows:

The text describes various routes for ocular drug delivery.

Intravitreal route:

The drug is administered through injections into the eye's vitreous fluid, a method that can cure various eye conditions, as illustrated in figure 2.

Intracameral route:

During surgery, an anesthetic substance is typically injected into the anterior chamber of the eye to deliver a medicine to either the anterior or posterior chambers.

Perilocular route:

Peril ocular steroid injection is a medication administration method that involves applying steroids to the eye to treat intraocular inflammation or swelling. [12]

Suprachoroidal route:

The administration method targets the eye's suprachoroidal space, which is the area between the choroid and the sclera.

Subconjunctival route:

The medication is administered to the mucous membrane, which includes the inner surface of the eyelids and the open region of the eyeball.

Topical route:

Eye drops are the most common ophthalmic dosage forms for topical medication administration in the eye, as they are easier to administer and less expensive than ointments, gels, and emulsions, which are used for treating anterior segment eye conditions.

Systemic route:

The blood-aqueous and blood-retinal barriers (BRB) are common barriers for the systemic delivery of ophthalmic drugs in the anterior and posterior eye segments. [13]

Classification of Ocular Drug Delivery System:

Ocular drug deliveries include semisolid gel, ointment, solid ocular inserts, liquid solution, suspension, and intraocular implant or injections.

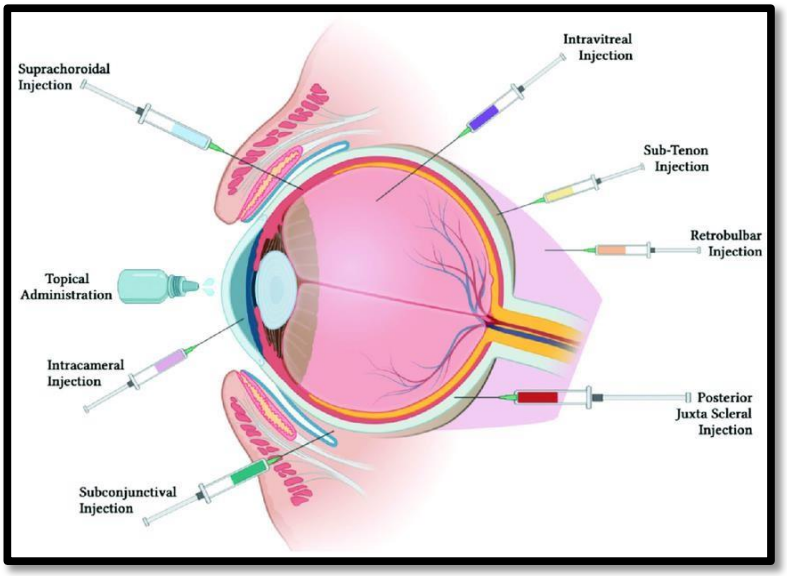

Figure 2:Intravitreal route

[13]

Advantages of ocular drug delivery systems:

The summary provides an overview of the benefits of ocular drug delivery systems.

1. Traditional systems can be prevented by providing consistency and precision in dosage rates, thereby ensuring the avoidance of pulsed dosing.
2. Drugs can be administered gradually and under the supervision of a healthcare professional.
3. The ocular bioavailability of medications is enhanced by the drug's efficient adhesion to the corneal surface, thereby enhancing the corneal contact time.
4. The ocular globe should be targeted to prevent the loss of ocular tissues.
5. They avoid protective ocular barriers such as drainage, lacrimation, and conjunctival absorption.
6. They enhance patient comfort, improve therapeutic medication performance, and boost patient compliance.
7. They offer improved delivery system housing.
8. They permit individuals to self-administer medications.
9. The absorption process is faster and there are fewer systemic and ocular side effects. [14]

Disadvantages of ophthalmic drug delivery systems:

The primary drawbacks of ophthalmic drug delivery systems include:

1. The medication solution and ocular surface have a brief contact time.
2. The bioavailability of the information is not sufficient.
3. The statement is about the issue of dissolved drug instability.
4. The text does not provide enough information to generate a summary. Please provide more details.

Limitations of ocular drug delivery:

Ocular drug delivery faces limitations such as unstoppable dosage forms during emergencies, vision interference, challenges in removing and placing dose forms, and occasional drug loss due to sleep or eye contact. [15]

Suitable characteristics of polymers:

A polymer is a crucial component in the production of in situ and preformed gels, with the appropriate characteristics for in situ gels being provided.

1. The polymer should be able to adhere to the mucosal membrane.
2. The task should be collaborative and not cause any irritation.
3. The statement does not indicate any toxic effects.
4. The statement should be tolerant.
5. The item must be biocompatible.
6. The polymer should be able to decrease viscosity as the shear rate increases to reduce viscosity during eye blinking.

Polymers used as in situ gelling agents are:

Gellan gum, alginic gum, carbomer, pectin, xylogulan, xanthan gum, and chitosan are all types of gum.

IN SITU GELLING SYSTEM:

In situ gel forming systems are drug delivery systems that are in solution form before being supplied to the body but undergo gelation in situ to create a gel triggered by external stimuli like pH or temperature. This method was first introduced in the 1980s and involves cross-linking polymer chains through non-covalent or covalent bond formation. Low viscosity liquids undergo phase transition in the conjunctival cul-de-sac to create viscoelastic gels due to polymer conformational changes in response to the physiological environment. The velocity of in situ gel formation is crucial due to the fluid mechanism of the eye producing a solution or weak gel between instillation and a strong gel. Both natural and synthetic polymers can be used to create in situ gels. [16-18]

CLASSIFICATION OF IN-SITU GEL

1. Based on physical stimuli. a. Temperature induced in situ gel system. b. pH induced in situ gel systems
2. Based on physical mechanism a. Swelling. b. Diffusion.
3. Based on chemical reaction a. Ion Cross Linking. b. Enzymatic Cross Linking.
4. Below describes the classification of in situ gel:-

1. **Based on physical stimuli**

   a. **Temperature induced in situ gel system:**

   Temperature-sensitive hydrogels and polymers change from sol to gel when the body temperature is adequate. Three types of temperature-sensitive hydrogels are thermally reversible gels, positively thermosensitive gels, and negatively thermosensitive gels. Some hydrogels are negative temperature sensitive, meaning they become insoluble when heated. Adjusting the temperature can improve gelling and prolong medication release. A change in temperature causes a change in hydration state, resulting in a volume phase transition when the polymer molecule's intra- and intermolecular hydrogen bonds prefer over water solubilization. Drug polymers, which are in solution form at room temperature and turn into gel at body temperature, can be used to produce this state. The upper critical solution temperature is the point at which certain polymers become soluble when heated. The volume phase transition results in intermolecular hydrogen bonding, making the molecule insoluble. [19-20] Poloxamer, a thermosetting polymer, increases contact time, drug elasticity, and sol to gel conversion when its concentration is increased. [21]

   b. **pH induced in situ gel systems:**

   Poloxamer is a thermosetting polymer that increases contact time and drug elasticity when its concentration is increased. This leads to a decrease in sol to gel conversion due to a pH shift. Polymers with a pH-dependent transition, such as carbopol and carbomer, release or receive protons based on the pH. When the pH rises, weakly acidic groups swell, while weakly basic groups do the opposite. When injected into the eye, the formulation's pH shifts from 4.4 to 7.4, causing it to transform from sol to gel. [17,19]

   Examples of cross-linked polyacrylic and carbomer derivatives are available.

2. **Based on physical mechanism:**

   a. **Swelling:**

   When materials absorb water from their surroundings and expand to create the appropriate area, in situ conversion of sol to gel may also occasionally take place. For example, myverol 18-99 is a polar lipid that, when swollen in water, forms a pyotropic liquid crystalline structure.

   b. **Diffusion:**

   The diffusion process of a polymer matrix, such as N methyl pyrolidine, occurs when the solvent from the polymer solution is absorbed by the surrounding tissues.

3. **Based on chemical reaction:-**

   a. **Ion Cross Linking:**

   Polymers can undergo phase transitions when multiple ions are present. I-carrageenan forms flexible gels with Ca2+, while k-carrageenan creates rigid, fragile gels with K+. Gelrite, an anionic polysaccharide, undergoes in situ gelling when mono and divalent cations like Ca2+,

Mg2+, K+, and Na+ are present. Divalent cations can induce low methoxy pectins to gel, while alginic acid gels when divalent or polyvalent cations are present. [17-20]

b. Enzymatic Cross Linking:

Natural enzyme-catalyzed in situ formation offers benefits over chemical and photochemical methods, such as efficient physiological function without hazardous substances. Hydrogels, which release insulin, are used in intelligent stimuli responsive delivery systems. When blood glucose levels rise, pH-sensitive polymers containing immobilized insulin and glucose oxidase swell, releasing trapped insulin. Mixes can be administered before gel formation, as varying enzyme dosage regulates the rate of gel formation. [5, 19, 22]

EVALUATION OF IN-SITU GEL

Clarity test:

Visual inspection of formulations is often used to assess clarity before and after gelling, using light or black and white backgrounds. A swirling motion is used to start materials moving, and undesired particles or turbidity development are monitored. [23, 24, 25]

Texture analysis:

The texture profile analyzer measures gel strength and application ease, assessing cohesion, firmness, and consistency. High adhesiveness value is necessary for gel to maintain close contact with mucous surface in vivo. [26]

pH:

The pH of ocular formulations significantly influences drug stability and solubility, ensuring patient comfort and stability. A digital pH meter is utilized for measuring this, ensuring no irritation during administration.[27] **Isotonicity evaluation:**

Ophthalmic medicines maintain isotonicity to prevent tissue damage or ocular discomfort. Blood is added to the formulation, examined under a 45x magnification microscope, and compared to commercially available formulations.[28,29,30]

Histological study:

The study examines the impact of in situ formulation on corneal structure and irritation. Corneas are extracted from a goat's eyes and incubated in the formulation for five hours at 37°C. The corneas are fixed in formalin and cleaned, then dehydrated in alcohol, submerged in paraffin, hardened into blocks, and examined under a microscope. Cross sections are cut and stained with H&E, and any changes are checked for.[31]

Drug Content:

The concentration of a formulation is determined by diluting 1 milliliter with 100 ml of distilled water, then measured using UV visible spectroscopy at 200-400 nm. [16]

Homogeneity:

The particle roughness can be examined under light by sandwiching the preparation between two glasses.

Gelling ability:

The gelling capacity and time of a formulation are determined by adding a drop to 2.0 ml of simulated tear fluid. [32]

Strength of gelling:

The gelling strength, measured by a Rheometer, is determined by the amount of gel in a beaker made from the "sol" form. A probe is pushed through the gel, and the depth of the gel surface's immersion is used to measure the weight on the probe. [33]

Rheological investigations:

The Brookfield viscometer measures the viscosity of in situ ophthalmic gels by increasing angular velocity from 0.5 to 100 rpm before and after gelation.

Test of Ocular Irritation:

The study uses male albino rabbits weighing between one and two kilograms to assess ocular discomfort using the modified Draize technique. The formulation is placed in a lower cul-de-sac, and its irritancy is measured periodically. The rabbits are then checked for eye redness, edema, and wetting. [34, 35, 36]

Drug release research in vitro:

Franz diffusion cells are used in in vitro drug release studies, where artificial tear fluid (ATF) is placed in the receptor compartment and a dialysis membrane is placed between the donor and receptor compartments. The assembly is kept on a thermostatically controlled magnetic stirrer, maintained at 37°C ± 0.5°C, and continuously churned at 20 rpm. The donor compartment is filled with 1 milliliter of the formulation, and samples are examined using HPL or UV spectrophotometer. [37, 38]

Studies of Accelerated Stability:

Sabouraud dextrose dissolves in hot water, and after autoclaving, organisms like Aspergillus fumigatus and Candida albicans are transferred to the media. A sample is taken and left for 30 minutes. The zone of inhibition is measured after a 24-hour incubation period at 25°C, and compared with positive and negative controls. [39]

CONCLUSION

In situ ophthalmic gels are a significant advancement in ocular drug delivery, particularly for drugs like latanoprost. These innovative systems use self-assembled nanomicelles to enhance drug bioavailability, therapeutic duration, and patient compliance. They also improve treatment efficacy in managing conditions like glaucoma. Despite the challenges in ocular medication administration, continuous technological advancements and understanding of drug absorption and disposal mechanisms have improved the effectiveness of ocular drug delivery systems.

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